REMARKS

Claims 1-3, 5, 7-16, 18, 19, 23-31, 33 and 34 are pending in the application. Claims 18, 19 and 29-31 are withdrawn from consideration. Claims 1-3, 5, 7-16, 23-28, 33 and 34 are rejected.

I. Response to Claim Rejections - 35 U.S.C. § 103

Claims 1-3, 5, 7-16, 23-28, and 33-34 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Hasegawa et al (Bull. Chem. Soc. Jpn. 2000, 73, 423-428) or Hisao et al (JP 8291106) in view of Ohuchida et al (US 6,201,021), Black (US 6,043,223), Toda et al (U.S. 6,608,221) and Takada et al (US 2002/0022738 A1).

Applicants traverse the rejection and submit that the claimed invention is not rendered obvious by the cited references, whether taken alone or in combination.

Independent claim 1 recites a medicament comprising (2R)-2-propyloctanoic acid or a salt thereof and about 1 to about 5 equivalents of a basic metal ion based on 1 equivalent of (2R)-2-propyloctanoic acid or the salt thereof, wherein the basic metal ion is supplied by at least one selected from a metal salt of phosphoric acid, a metal salt of carbonic acid and a metal salt of sulfurous acid, and optionally a metal hydroxide.

The present invention relates to a precursor for injection comprising (2R)-2-propyloctanoic acid. In the present invention, the problems of clouding when (2R)-2-propyloctanoic acid is diluted in order to formulate an injection appropriate for administration and difficulty of long-term storage are solved by allowing for the coexistence of about 1 to about 5 equivalents of the basic metal ion based on 1 equivalent of (2R)-2-propyloctanoic acid or a salt

thereof, ass described in the specification of the present application in the paragraph bridging pages 2-3. The present invention is not merely that solubility of (2R)-2-propyloctanoic acid can be increased by mixing it with a sodium hydroxide or by making it to be sodium salt. Which appears to be the Examiner's position.

The Examiner asserts that Black discloses a method wherein sodium phosphate is added in order to stabilize the drug compounds and peptides. However, Applicants submit that there is no description in Black at all of sodium phosphate and stabilization.

Black, teaches that Zaprinast, which is a cyclic GMP phosphodiesterase inhibitor, cannot be dissolved in physiological saline and it is dissolved by adding sodium hydroxide. When sodium hydroxide, which is used for dissolving Zaprinast in Black, is added to (2R)-2-propyloctanoic acid used in the present application, it can be easily expected that the sodium salt of (2R)-2-propyloctanoic acid can be made. Additionally, the fact that solubility in water increases by making (2R)-2-propyloctanoic acid to be sodium salt is described in the paragraph bridging pages 2-3 of the present application as described above.

However, Applicants submit that the problem solved by Applicants is not that (2R)-2-propyloctanoic acid which is insoluble in water is dissolved in water by adding sodium hydroxide. The inventors of the present invention found for the first time that there are problems that (2R)-2-propyloctanoic acid dissolved by sodium hydroxide becomes clouding when diluted in order to formulate an injection appropriate for administration and that insoluble allotrio is generated during storage. Thus, the inventors accomplished the present invention as a means to solving these problems. Therefore, the present invention is not rendered obvious by the art cited

by the Examiner which merely relates to dissolution of (2R)-2-propyloctanoic acid with sodium hydroxide.

Moreover, since the Examiner supposes that sodium phosphate is included in phosphate buffered saline (which Applicants do not concede), even if the teachings of Black were considered in combination with the cited references, the present invention would not have been obvious. Exactly, 0.09% phosphate buffered saline is used as a carrier in an intravenous injection in Black. However, when the amount of the active ingredient and the basic metal ion in the pharmaceutical preparation of Black is calculated, the preparation is a "preparation which contains about 0.085 to about 10715 equivalents of the basic metal ion based on 1 equivalent of active ingredient, bradykinin". Therefore, based on the equivalent number, the range of equivalents of the basic metal ion is very broad. Namely, more than 12,000 times of the basic metal ion based on 1 equivalent of active ingredient are included in the preparation in Black. On the other hand, the present invention solves the problems of clouding when diluted in order to formulate an injection appropriate for administration and difficulty in long-term storage by allowing coexistence of very narrow range of about 1 to about 5 equivalents of the basic metal ion based on 1 equivalent of (2R)-2-propyloctanoic acid or a salt thereof. Thus, a person skilled in the art would not have had a reasonable expectation of success of arriving at the claimed invention involving only a range of about 1 to about 5 equivalents without indication of the problems based on the teachings of Black which teaches a range of more than 12,000 equivalents. Therefore, for at least this reason it cannot be said that the present invention is obvious.

Additionally, the present invention solves the problems of clouding when (2R)-2-propyloctanoic acid is diluted in order to formulate an injection appropriate for administration and difficulty of long-term storage by changing the amount of the basic metal ion according to the amount of active ingredient. On the other hand, a predetermined amount of the basic metal ion is used as a carrier for any concentration of the active ingredient in Black. That is, the same amount of a basic metal ion is used regardless of the concentration of active ingredients in Black. Thus, essentially, the technical concept and features of Black are totally different from that of the present invention. Even if the disclosure of Black were combined with (2R)-2-propyloctanoic acid, it becomes different invention from the present invention, i.e., the present invention would not have been achieved. For, this additional reason, the present invention is not rendered obvious over the cited references.

The Examiner asserts that Takada et al teaches a method wherein at least one pH adjuster selected from tri-sodium phosphate, a hydrate thereof, sodium hydroxide or potassium hydroxide is added to solution. In Takada, a pH adjuster is used in order to increase the solubility of agents. However, the characteristic features of the present invention are not to increase in solubility of (2R)-2-propyloctanoic acid. The Applicants understand that solubility of (2R)-2-propyloctanoic acid increases when sodium hydroxide is added to (2R)-2-propyloctanoic acid as stated in the paragraph bridging pages 2-3 of the specification. However, the Applicants found a problem in the solution obtained by such a method of clouding when (2R)-2-propyloctanoic acid is diluted in order to formulate an injection appropriate for administration and difficulty of long-term storage and achieved the present invention by regarding these as the problems to be solved in the

present application. Therefore, it cannot be said that the present invention is obvious based on disclosure of Takada et al combined with the cited references.

Additionally, as pointed out by the Examiner, Hasegawa et al discloses an optically active (2R)-2-propyloctanoic acid which is a valuable therapeutic agent for neurodegenerative diseases such as Alzheimer's disease. Hisao et al discloses a salt of optically active (2R)-2-propyloctanoic acid (which is (R)-(+)-1-phenylethyl amine salt and the like). Ohuchida et al relates to a pentanoic acid derivative and general salt including a basic metal ion. Toda et al discloses mixtures including a mixed solvent of i) (2R)-2-propyloctanoic acid, ii) sodium hydroxide and iii) n-hexane/acetic acid ethyl can be obtained in production steps of (2R)-2-propyloctanoic acid. But none of these references teaches , suggests or even recognizes the problems solved by Applicants.

At best, from the combination of Hasegawa et al, Hisao et al and Ohuchida et al and Toda et al, and arbitrary salt of (2R)-2-propyloctanoic acid can be obtained. However, the present invention does not relate to a "salt".

Black does not remedy the deficiencies of the Hasegawa et al, Hisao et al, Ohuchida et al, Toda et al and Takada et al for the reason discussed above. Therefore, the present invention cannot be expected from any combination of the cited references. None of the references cited by the Examiner teaches, suggests or even recognizes the problems of clouding and the generation of insoluble allotrio within the solution during long term storage solved by the present invention. Even further, none of the cited references discloses, teaches or suggests the use of metal ions in combination with (2R)-2-propyloctanoic acid to solve the problems of clouding and the generation of insoluble allotrio within the solution during long term storage. Thus, it is only

with improper hindsight reasoning that the Examiner could have arrived at a conclusion of obviousness.

Also, the Examiner's reliance on case law is misplaced. The Examiner is correct in stating that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. However, the Examiner has failed to provide such a teaching, suggestion or motivation in the references or knowledge available in the art.

The Examiner is also correct in stating that the prior art must be considered as a whole. However, the claimed invention must also be considered as whole. In this case, the Examiner is not considering the claimed invention as a whole. Instead, the Examiner is improperly asserting obviousness of only one individual element of the claimed invention, i.e., the metal ion source. There is no teaching, suggestion or even recognition in the art of the use of metal ions in combination with (2R)-2-propyloctanoic acid or of the problems of clouding and the generation of insoluble allotrio within the solution during long term storage with (2R)-2-propyloctanoic acid liquid or semi-solid formulations as mentioned in the present specification at pages 2-4. Therefore, the prior art as a whole does not teach or suggest the claimed invention as a whole.

Since the Examiner has not made a *prima facie* showing of obviousness, it is not necessary for Applicants to provide evidence of unexpectedly superior results as requested by the Examiner.

II. Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

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